



THE SCIENCES

PUBLISHED BY
THE NEW YORK
ACADEMY OF
SCIENCES



THE INHIBITOR INHIBITED

Monoamine oxidase inhibitors (MAOI), more easily and dramatically called "psychic energizers" from the potency of their chemical action on mental functions and psychic states, may be likened to fire or atomic energy — they are blessing or curse depending upon how they are used and by whom.

These inhibitors are believed to achieve their effects by deactivating an enzyme known as monoamine oxidase (MAO). This enzyme, in turn, normally breaks down that group of chemicals within the body classed as monoamines, which includes serotonin, epinephrine, norepinephrine and other substances one or more of which are thought to have "psychic effects."

When a variety of stimuli cause these monoamine substances to be released in varying quantities from the cells in which they are stored, the enzyme monoamine oxidase regulates their actions. To increase the blood levels of the monoamines, three alternative procedures are available: The mechanisms which trigger their release from the cells can be stimulated; their volume can be supplemented from an external source; their rate of deactivation by the enzyme can be reduced. The monoamine oxidase inhibitors serve the latter purpose by doing what their name implies — they neutralize the enzyme or, in effect, inhibit the inhibitor.

This much is demonstrable concerning the metabolism of monoamines, but precise and equally demonstrable explanations for the end effects on mental conditions are lacking. These effects are pronounced, however, as was discovered in one of the more remarkable episodes in clinical experience. In the early 1950's, ipron-

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iazid was administered to a group of hospitalized tuberculosis patients. A state of euphoria was induced by the drug that caused previously lethargic patients to literally dance in the halls of the hospital. When this was traced to the monoamine-oxidase-inhibiting properties of iproniazid, a new era in medical research began.

Thousands of compounds have been screened in the search for more effective monoamine oxidase inhibitors. With each experimental and clinical enlargement in knowledge of the chemistry of the psyche and mental illness, the chemical approach to mentation has gained new impetus.

The usefulness of these agents in certain mental disturbances prompted their extensive utilization before the most compelling indications for or against their use was fully understood.

At the conference on Amine Oxidase Inhibitors conducted by The Academy to bring together the relevant findings concerning these drugs and their use, one of their limitations was summed up by Dr. Sidney Merlis in the statement: "... these compounds have a rather narrow margin of safety...."

One of the chief dangers associated with the MAOIs is liver damage resembling that caused by viral hepatitis. Autopsy examinations show no difference in the histologic pattern of tissue destruction they are capable of causing and that produced by viral hepatitis.

The liver, however, releases large quantities of the enzyme transaminase at the least hint of injury. Careful monitoring of transaminase levels in the blood permits regulation of MAOI dosage to preclude administration of amounts likely to cause destruction of liver tissue.

The major problem that remains is when and how to use these compounds effectively. That they do relieve depressions has been fully established clinically, but it is also true that they do not relieve all depressions. The potential causes of depression are so numerous, and the behavioral effects so similar, that it is difficult to identify cause with effect on grounds to which investigators can agree.

The usual method of arriving at a diagnosis is the psychiatrist's necessarily subjective evaluation of the patient's behavior patterns. This is a source of confusion, as published investigative reports frequently show discrepancies from study to study in evaluations

of MAOIs in the treatment of presumably identical conditions. The differences are often traceable to a lack of uniformity in methods of patient classification, although the terminology may be the same.

The intention is to work out eventually a new classification of mental disorders based upon causes rather than symptoms. In the meantime, the MAOIs present an opportunity for the classification of certain of these disorders on an evaluation of their response to chemotherapy.

The psychic energizers or antidepressants act in a manner reverse to that of tranquilizers — although both are capable of lowering blood pressures and of enhancing the effects of other drugs. At The Academy conference, David English presented a concept of mental condition as a continuous vertical line running from the depressed state through the normal balanced range to the manic state. The MAOIs are intended to raise the patient from the depressed state into the "zone of normality," the tranquilizers to lower him into it from the manic level.

Schizophrenia fits nowhere on this line. It is still largely a mystery disease (some authorities believe that the schizophrenia seen in childhood is a different disease than that encountered in adult patients), but the belief is growing that it is a metabolic disorder. Tranquilizers are frequently used as palliatives. In mild cases, an MAOI has been found to be useful. Dr. English has worked with combinations of an MAOI and a tranquilizer, with the proportions of each scaled to individual patient requirements and reactions.

Many investigators continue to believe electroshock therapy more valuable in the treatment of depressions than the MAOIs, although this attitude is far from universal. The combination of MAOI and electroshock has been shown to produce a more rapid relief of depression than either used alone.

The possibility exists that the effect of the MAOIs may not be a result of their action on the metabolism of the known monoamines. Sidney Udenfriend points out that the MAOIs release all kinds of amines in the body. Tyramine, for example, is found in markedly increased amounts in the urine after MAOI administration, as are other amines. It seems probable that these amines are normally produced in the body, but methods for finding them have not, for the most part, been available, even

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though they may be present in amounts equivalent to those of serotonin and norepinephrine. A neurophysiologic explanation of the activity of the MAOIs must await the development of more information concerning these amines, their quantities, and their actions.

Further, most of the MAOIs investigated are members of the hydrazine group. Any mechanism that may be postulated for MAOIs generally may turn out to be relevant to only some - or none - of the many MAOIs that are not hydrazines.

There is also some lack of correlation between the observed behavioral and systemic effects of the MAOIs, even in patients with the same type of disease. But the by-products of the metabolism of the monoamines have a tendency to accumulate when an MAOI is administered, and may possibly account for the observed effects. There is also the possibility that they are the result of the direct action of the MAOIs rather than due to indirect effects, as is presently assumed.

Anthony Sainz reported to the conference that he has been able to obtain remissions with phenelzine (one of the hydrazines) despite the fact that phenelzine did not alter the blood levels of the MAOIs. He, however, tested blood from the jugular vein, and pointed out the possibility of intracerebral changes that were not detectable by this method.

G. J. Sarwer-Foner summarized his view of the field with the statement: "One thing is certain: Although monoamine oxidase inhibitors are certainly interesting and possibly represent an important step forward in the study of cerebral metabolism and, possibly, also towards an elementary knowledge of the biochemistry of emotion, it is naive in the extreme to attribute to this one biochemical action a one-to-one direct, important, or specific action in depressions.... There is too much that cannot be accounted for by this ... hypothesis."

Also, he added that "It is for the biochemist and the neurophysiologist to decide what role monoamine oxidase inhibition plays in cerebral metabolism. Such knowledge is an interesting and necessary step in neurobiochemistry. It is the role of the clinician to demand that theories, biochemical or otherwise, fit the observed and verifiable clinical facts before they can be seriously entertained.



Psychological Too

The capacity for effective communication, apart from the use of the technical devices available for that purpose, is a factor of understanding. The slogans and word symbols that carry moral and ethical values appropriate to one culture may appear as absurdities in another.

In a paper presented before The Academy's Division of Psychology, Professor Wayne Dennis of Brooklyn College stated that the U.S.-trained psychologist who attempts to utilize the psychological methods developed out of the cultural patterns of Western countries will find them inadequate for studying national character in other cultures. "When translated into the languages of non-Western nations, they seem bizarre and inappropriate."

While resident in the Middle East, Professor Dennis devised a test to measure comparatively the impact of national culture on group personality. He used the question-and-answer method. Questions were designed to be of universal or quasi-universal applicability, such as: "What is so and so for," and "Why does a person run?" He selected as his subjects 12-year-old children living in Bagdad, Beirut, Cairo, Damascus and Tehran to represent a Middle East background. Upper-middle-class children attending the American Community School in Beirut represented the Western culture.

Responses were classified into four categories, and interpreted in terms of personal goals and motivations.

Category 1 (Benevolent): "Responses referring to helping others, taking care of others, or referring to love, loyalty, affection or friendship."

Category 2 (Malevolent): "Responses referring to ill will, injury, or the threat of injury whether by the respondent or others. Included are references to hitting, striking, fighting, fear, distrust, hatred, danger, disaster and calamity."

Category 3 (Hedonistic): "Responses referring to

objects of actions as sources of pleasure or displeasure."

Category 4 (Religious): "Responses referring to the deity or to religious books, religious leaders, and religious rules, practices and prohibitions."

Responses were scored as benevolent to such questions as "why does a person run?" if the reply was "to help someone"; malevolent if the reply was "because he hurt someone"; hedonistic if "because he is playing"; religious if "because God doesn't like a lazy man."

Professor Dennis stated that the "difference in the benevolence and malevolence scores in part reflect nationalism and patriotism. Patriotism in Tehran is expressed largely in terms of wishing to help one's country whereas in Cairo it is more commonly expressed as a desire to defeat one's enemies. However, a general dimension of friendly-unfriendly world view appears also to enter into the benevolence and malevolence scores. These scores do not seem to be direct opposites. The American subjects, for example, are low in malevolence but not particularly high in benevolence."

Tehran students scored highest in the benevolence category, Cairo the lowest, and the Americans scored on the intermediate level.

The lowest malevolence scores were recorded by Americans, while among the Middle Eastern nationals those in Tehran scored the lowest malevolence quotient. Not all malevolent answers given by the Arabic students were of a nationalistic patriotic nature. A lion, for example, was associated with killing people, and a storm was seen in terms of destruction. The groups with lower malevolence scores related a lion to a zoo, and a storm with rain. It was apparent, Professor Dennis stated, that a view of the world as being friendly or unfriendly "... enters into the benevolence and malevolence scores."

Americans were found to score highest in hedonism and the Middle Easterners the lowest. This result correlated with the widespread belief that Americans are "pleasure-seeking and self-determining in their actions." American answers were based upon "individual freedom of choice as well as upon love of pleasure." The Middle Eastern child is taught to be serious and the dominant childhood motif is duty rather than pleasure - duty to family and to school.

In religious scores all groups were found to be low. This apparently presents evidence that religious thinking is not a major consideration in explaining the functions of familiar objects and the motivation of common actions.

In Beirut, the twelve-year-old group was further

divided into Christians, Moslems and Jews, all of Middle Eastern ancestry. No significant differences were found except that the Jewish children scored high on hedonism. This was attributed to the fact that the Jewish school they attended was patterned after the French educational tradition and many of the teachers were European. There was no other apparent reason for the Middle Eastern Jews to make a high hedonistic score.

Additional data was drawn from the tests when they were applied to students in secondary schools and colleges, to skilled technicians, to illiterate laborers, and to Bedouins living in the Syrian desert. It was found that differences were slight in the benevolence-malevolence scores. "But neither education urban living seemingly served to reduce hostility or induce a more friendly world view." Hedonism, however, showed a definite relationship to education, social class or both. College students made higher scores than secondary ones and they in turn were higher than the primary students. Hedonism "appears to be a function of education rather than age since noncollege adults have relatively low hedonistic scores. Among the Bedouins, hedonistic scores are also low.... Low hedonism represents a cultural tradition of long standing since the Bedouins are the oldest of the extant Middle East groups."

With regard to religious scores, the Bedouins scored highest. They still retain a strong religious tradition that presumably prevailed once in Arab cities. Conclusions were drawn that "The pervasiveness of religious ideas in everyday thinking, which probably once existed among Jews, Christians, and Moslems has largely disappeared in the Middle East. Today it exists among Bedouins and probably among a few other ultra-conservative groups ..." "Hedonism ... is highest where Westernization is highest. Benevolence and malevolence do not seem to be fundamentally related to Westernization. The most Westernized Arab cities, Cairo and Beirut, and the most educated citizens ... are as high in malevolence as are Bedouins. Education and Westernization per se do not seem to reduce hostility."

Professor Dennis' experience again illustrates the fallacy of attempting to interpret personal motivations, social and political attitudes in one culture by a process of analysis rooted in another. He suggests that the universality of the technique he worked out for use in the Middle East "... may prove useful in the future repertoire of the psychologist who wishes to make comparisons between groups differing greatly in language and culture."

of Microsurgery

The art of microsurgery is practiced on a cellular scale. Microinjectors used in the dissection of cells can measure and control fluid volumes of less than one-fifty-millionth of a drop, and the hooks, scalpels, needles, forceps and scissors used in manipulating cells and parts of cells have comparable micro-characteristics.

"With these highly precise mechanical devices, known as micromanipulators," Dr. M. J. Kopac stated in an address before the annual meeting of The Academy, "one can insert a needle or a pipette into a cell with delicacy so exquisite and precise that a part of a cell or a nucleus can be removed and implanted into another cell or nucleus."

There are several designs of micromanipulation equipment but the principal distinction is in the technique — screw- or pneumatic-activator — of operating the micro-instruments. Nearly all the tools are made of finely drawn glass

Among its achievements, "microsurgical study of living cells has firmly established the reality of chromosomes, nucleoli, spindle fibers, nuclei, mitochondria, and ... other subcellular structures," and it has helped define the structure and function of the cell surface and the extraneous coats. The last-noted have been shown to serve primarily as protectors; without them, a slight trauma to the surface of the cell might destroy the entire cell.

Microsurgery has shown that cellular proteins are highly integrated with subcellular structures and will behave as ordinary proteins only as a sequel to disintegration of those structures. This finding emerged from experiments with oil drops injected into the cytoplasm of living cells. The oil drop remains intact and spherical unless the nucleus is punctured, in which event the cell lyses (often in a matter of seconds) and the oil drop

loses its spherical shape as its phase boundary becomes crinkled. This crinkling, called the Devaux effect, results when proteins accumulate and undergo surface denaturation at the oil-water interface.

Because of the high susceptibility of the nucleus to damages, exceptionally delicate techniques are required to transport portions of the nucleus of one cell to the nucleus of another. But the effects observed in studies of transplantations of nuclear material are of special interest, especially for their bearing on genetic processes. If transplanted so that it becomes part of the nuclear complex of a host cell, the nucleolus, for example, serves as a genetic marker that can be followed in the successive generations of the altered cell. Transplantations of portions of chromosomes or of nucleolar organizers also offer precise ways of studying gene action and cell differentiation processes.

Microsurgical techniques gained their first major impetus in the work of Chambers in the early '20s, and since then, as a result of repeated advances in biological knowledge as well as in mechanical and optical instrumentation, have reached a point where investigators ask about limitations. Dr. Kopac expressed the view that "in so far as delicacy of micropositioning is concerned, there is no limit." Moreover, although micromanipulators already operate at the limits of optical microscope resolution, these could be improved. Nevertheless, there do appear to be limitations on the minimum size of pipettes — one of the most versatile tools of the technique. Beyond 0.5μ inner diameter, hydrodynamic problems arise which may be insuperable. Furthermore, superfine micropipettes lack the strength needed to penetrate certain tough cellular membranes.


Long experience has shown investigators that, for effective work, cells should be at least 10 times and preferably 100 times larger than the micropipettes being used to study them. The comparable optimum size of experimental material when the smallest practicable micropipette is used would then be in the range of 5μ , a dimension that excludes bacteria, which rarely exceed 1μ . The situation is exasperating because to attempt to duplicate or approximate the natural microinjection processes of bacteria would be a most interesting challenge. In one variety of conjugation, bacterial viruses transfer viral nucleic acids from "male" to "female" in quantities equal to no more than 5 to 10 bits of genetic formation.

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WOMEN IN SUBURBIA

"The crabgrass has taken over, the barbecue chimney has an unused look, the aluminum chairs in the backyard are no longer in friendly groups." In short, suburbia has become for many women a Paradise Lost, Professor Nanette Scofield of Columbia University reported before The Academy's Division of Anthropology.

The realities of daily commuting schedules, endless mortgage payments, mounting school taxes, the car pool, and increasingly city-like conditions without urban conveniences have eroded the vision of the suburban idyl. Worst of all, a once-appealing homogeneity of kind, interests, income, and enthusiasms has been reduced to dullness "...the sameness of thinking and that same every-Saturday-night party with its little black dresses, each with a pin at the corner of its low-cut neck," as it was stated by one suburban sufferer.

"What Webster defines as the intellectual content of civilization and the Romans called *humanitas*, we give the less happy phrase of 'culture.' If culture flowers in the city, it withers in the suburbs despite intensive and anxious nurturing. Schools for adults flourish throughout the suburbs but...courses that give homework do not attract students, so that the so-called intellectual courses become lectures, and the sell-out courses are bridge, golf, and woodworking. Women take a variety of day courses, with little genuine intellectual content. Dilettantism thrives in suburbia," Professor Scofield said.

The role of woman in suburbia has become increasingly confused. Married women are returning to work at such a rate as to constitute the largest source of new workers. "This trend changes the climate of opinion for the return to work of women of all economic levels." Dr. Scofield cites Margaret Mead on the conflicts engendered in women by underutilization of their education and potentials. "We have the striking paradox of women who are educated like men and who can do

most of the things men do but who still are taught to prefer marriage to any other way of life.... In this paradox lies much of the confusion for women today."

"In addition," Professor Scofield reported, "for women who moved to the suburbs ten years ago, a new level of life is beginning. Now, for the first time, they can see a future where the family plays a diminishing role. At the same time, society encourages them to cut apron strings once that family is grown."

How is all this to be resolved? "In work for gain? In volunteer work with a purpose, or volunteer work that is frenzied activity? In taking courses with the object of professionalism or self-fulfillment, or both? In too many courses, none in depth?"

Sociologist Theodore Caplow is quoted as having found "... that while the housewife in her middle years may have no personal economic need, she has the psychological need to justify herself...." The Department of Labor, on the other hand, reports that "...very few women are working just for the satisfaction of having a job." And David Riesman sees women "...being driven out of many areas in which they formerly occupied their leisure with amateur competence."

Professor Scofield mailed questionnaires to 200 suburban, college-educated women, 25 to 35 years of age, with annual incomes in excess of \$25,000. More than 50 per cent responded. "This fact alone may have as much significance as the validity and value of the questionnaire itself."

The study, a limited survey, "...represented an attempt to formulate, define, and explain the problems faced by married women living in a suburban community...." Both unrest and *unreality* were reflected in the responses, as there was a tendency to give those answers the women thought proper.

"More than half of the women plan to work; 13 per cent immediately, the rest in five to 15 years. Sixteen per cent do not know their plans; 32 per cent know they will never work." Out of the total, 75 per cent felt that they were inadequately prepared for work, and 80 per cent of this group plan to return to school for training.

It also appeared from the survey that "women will be more likely to work if their mothers have worked for gain or if their mothers have been very active volunteers." And those whose college majors were in arts and sciences felt more need for guidance than those who had majored in education, psychology or business courses.

At the time of the survey, 62 per cent of the respondents were doing volunteer work, of "the one-day and under variety." Another 45 per cent were taking courses, mostly of a self-improvement nature. Very few were taking courses toward a degree.

Professor Scofield found it "...significant that 50 per cent of these women, from an upper-economic group, see themselves in remunerative work. In other generations these were the women who carried the brunt of charitable work. Charity depended on them, and they themselves felt a moral obligation. This moral obligation now has apparently disappeared, replaced by the psychological need to be economically productive." This reflects the social attitudes of our time: "We are an economic society and all things are valued in terms of money; and women, educated as men are educated, have been given the same objectives."

But the suburban woman "looking for a career, paid or volunteer, meets many obstacles." Volunteer activities often reach the "dead end" of fund-raising. There are few available paid jobs that can make use of her talent, and if she wants to return to school to retrain herself for the day when she will be employed, time places a severe limitation on the schools she can attend. Her counterpart in the city has both greater volunteer opportunities with the necessary status values, graduate schools within easy reach, more part-time job openings, and more acceptable work categories.

For many women, suburbia is a dilemma. The raising of children has become more rather than less complex than in the city. She is bored and "counteracts loneliness with too much belonging. How will she fare in the future? Will she 'sink back' into indifference or, striking out in all directions, hope to stumble on one right way? ...Given proper status, volunteer work could be an answer; given proper cultural outlets, many women would not feel the need for a job; given an understanding society, more and better part-time jobs could be made available." And Professor Scofield's report points out the necessity for a reduction in the degree of fantasy to which suburban women fall prey in their searching "for something intangible" in their occupational choices. "If a woman does not view her career from the perspective of her own and her family's needs and desires, she is unthinking and unrealistic."

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